DRUG DELIVERY: REAL-WORLD UPDATES AND FUTURE OUTLOOK

A roundtable discussion of solutions on the market and in the pipeline.

BY RICHARD A. LEWIS, MD; E. RANDY CRAVEN, MD; L. JAY KATZ, MD; JAMES KATZ, MD; AND SAVAK TEYMOORIAN, MD, MBA

Richard A. Lewis, MD (R.A.L.): The bimatoprost implant (Durysta, Allergan) was recently approved by the FDA, and the approval of a sustained-release travoprost implant (iDose, Glaukos) is impending. Many initiatives in glaucoma resemble those that took place previously in cardiology. Cardiologists started implanting drug-eluting stents years ago, and glaucoma specialists are likely to follow suit. However, several challenges associated with drug delivery exist, from navigating the regulatory pathway to determining the best drug, device location, and postimplantation strategy. Randy, what are your thoughts on the evolution of drug delivery in glaucoma?

E. Randy Craven, MD (E.R.C.): It has been a long journey. When I first started practicing, pilocarpine was one of the main drugs in glaucoma. However, we struggled with how to make it work better because it has such a short half-life. We developed different drop formulations and inserts, followed by a gel. We tried subconjunctival injection. We also tried injecting anecortave acetate, but we would hit the aqueous veins. The drug would go into the anterior chamber and fill it up. We explored many methods of drug delivery over the years because the advantages always looked appealing.

One day more than a decade ago, Rick and I received a call from a head researcher at Allergan asking us to come to the lab to work on drug delivery. It was exciting to test the concept and see that we might finally be able to put medications exactly where they should be and address disease that way. It has been a great ride ever since.

R.A.L.: As mentioned earlier, the next drug delivery device to be approved is likely the iDose. Jay, can you update us on why travoprost was selected for this device, where you see the product going, and whether other drugs might be added to it?

L. Jay Katz, MD (L.J.K.): Drug delivery is such an exciting area in general, and it could transform how we treat glaucoma. The iDose platform is based on the iStent technology (Glaukos). It features a titanium canister that is anchored in the angle, where it elutes travoprost. This drug was chosen for a number of reasons: Prostaglandins have a long track record, we know how they work, travoprost is very effective for lowering IOP, and it could be put into the canister and eluted in a way that we thought would be beneficial for lowering pressure from within the eye.

The outcomes have been encouraging. As shown by the phase 2 results,[1] the average IOP reduction was about 8 mm Hg, which is akin to what was seen with topical drug delivery. Per the study protocol, patients whose IOP measured 18 mm Hg or higher needed to be rescued with medication. At 3 months, 80% of eyes were controlled without any rescue medication. At 1 year, more than 50% were still controlled without rescue medication. At 2 years, about one in three eyes was controlled without additional medication. These results have encouraged further work; a phase 3 trial has enrolled more than 1,000 patients, and we are anxiously awaiting the results of that investigation.

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R.A.L.: Do you think the iDose labeling will be for 1 year and then the device can be replaced at the 12-month mark?

L.J.K.: That is still evolving. One of the prospects is that the canister can be replaced, whatever the timeframe might be. Safety is also critical when looking at an implant being placed in the eye for that period of time. Fortunately, the safety profile of the iDose is favorable, including when looking at the cornea and endothelial cell counts. Those results support the possibility of exchanging the implant when the load has been depleted.

James Katz, MD (J.K.): As a cornea and cataract surgeon, my main concerns are the endothelium in the long term and flow differences in the anterior chamber. Could those be issues? Where is the iDose being placed?

L.J.K.: The canister is anchored in the trabecular meshwork. It does not touch the cornea.

J.K.: I like the idea of having the ability to remove the insert because sometimes these devices move around. The fact that it can be removed and replaced with another insert sounds beneficial for the health of the eye.

R.A.L.: We cannot deny that reimbursement drives behavior. Reimbursement seems to be good for Durysta, and it will probably be in the same ballpark for iDose, although Durysta can be placed in an outpatient procedure, whereas the iDose will likely have to be placed in an OR setting. Sev, how do you see this playing out?

Savak Teymoorian, MD, MBA (S.T.): When we talk about glaucoma interventions, it comes down to what the physician thinks is the right approach and what they are most comfortable doing. When colleagues ask whether to do Durysta in the office or at the surgery center, I say, "Whatever is best for you and your patients." This will differ based on practice patterns and patient populations. I do most of my Durysta cases at the surgery center because I have found this setup to provide the most efficient patient experience.

It used to be that, when treating a patient for glaucoma, there were two options: drops or trabeculectomy/tube shunt surgery. Now it is possible to use a combination of approaches. Our job is to take the options available and devise a solution that works well, but there will be limitations. Glaucoma is a chronic disease, and eventually treatments fail. That does not mean that they are not good options. We tend to get lost in the idea that failure is the opposite of success when, in reality, it is the pathway to success. I encourage those thinking about implementing drug delivery systems in practice to feel comfortable doing so. You are not failing if a patient needs an additional or alternative treatment—it is all part of their overall success.

R.A.L.: This is an interesting age because we have drug-eluting implants, steroids that can be injected in the eye, and new ways of delivering drugs such as with the Optejet (Eyenovia) and other instruments in clinical trials now (Editor's note: For more on delivery devices, see "Drop Aids" on pg 54). It is in a state of flux, and perhaps we will get past eye drops. These newer ways of delivering drug will be more customized.

E.R.C.: I think we will see an era of interventional care be a part of what we do early on because we all real-

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ize the shortcomings of drops. The happiness of people using Durysta is high. Ophthalmologists are happy with how their patients are doing, and patients are happy with their experience. Plus, a lot of them have a duration of effect that goes on for a long time. It is curious why that is if all the medicine is eluted out of the device.

R.A.L.: There is a tissue remodeling effect, and that came up with Durysta.

E.R.C.: Robert N. Weinreb, MD, has looked at the effects of bimatoprost on the uveoscleral outflow pathway and found evidence of increased spaces in the ciliary muscle.[2] The exact mechanism that provides this duration of effect is unknown, and it is variable. Why it happens is a mystery, but I'd like to find out.

R.A.L.: This also presents an opportunity for the posterior segment. We now have drug delivery systems for the back of the eye; it is a question of getting the right drug to deliver. What are your thoughts regarding neuroprotection? Memantine has been tried as a pill, but it did not work well.

E.R.C.: Brimonidine may work intravitreally for neuroprotection. That is a hard endpoint to achieve because it takes a long time to see the effects of neuroprotection, but that is an area of unmet need. We've tried putting medicines in the vitreous cavity, but that approach doesn't have the same effect as intracameral delivery. You don't get the same bang for the buck when you put the medication in the back of the eye, probably because of the targets it must reach.

J.K.: Intravitreal is one delivery route, but there are others, such as intracanalicular, that can be used to elute these medications and enable easier administration. Are they as effective? Maybe not, but we can adjust the dosage. There are also areas for drug delivery within the conjunctival space.

L.J.K.: Neuroprotection is a great goal, but it is difficult to prove to the FDA and therefore have a commercial entity emerge. I think it will be possible to safely put drugs inside the eye that may not provide a therapeutic response when used topically, either due to poor penetration or tolerability, but may lower IOP when placed internally. Many patients have given up on certain topical drugs that effectively lower IOP because of side effects or problems with compliance; now, there is an avenue for placement within the eye that circumvents these issues. Drug delivery alternatives to topical administration have great promise as an exciting new therapeutic approach, enabling use of drugs that were previously abandoned because of various problems.

R.A.L.: Look at Rho kinase inhibitors. If they didn't have the redness side effect, the efficacy would win the day.

S.T.: For us in glaucoma, we often think we know something and later realize we do not know as much as we need to know. Now, we are realizing the opportunities that we can exploit, but we will have to work collectively to expand this area.

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R.A.L.: Device-based MIGS procedures will allow the use of drug delivery stents. I see us going down this path where we will be doing MIGS procedures with drugs. The question is who starts that effort. It is a challenging regulatory process and a challenging endpoint efficacy process, but it can be done.

E.R.C.: Intraocular gene delivery will also be an area of expansion.

R.A.L.: Is anyone seeing endothelial problems with Durysta?

E.R.C.: The compound and the delivery system seem to be safe to the corneal endothelium. The mechanical effect of multiple implants is the potential concern.

R.A.L.: What would happen if you placed a drug implant in a patient who has a Xen Gel Stent (Allergan) or a Hydrus Microstent (Alcon)? In the Durysta studies, there was movement of the implant to areas of less resistance.

J.K.: By definition, you are affecting the direction of flow, so there is movement. It is somewhat of a concern to the endothelium. Studying this out past 5 years is important, yet we have not seen any issues in the long term.

E.R.C.: Have you placed any Durysta implants in post-MIGS patients, Sev?

S.T.: I have. When implanted, the device hydrates up to about 150%, so migration does not occur. However, the implant has a logarithmic decay, so once it gets smaller, this could become a problem. For those doing both procedures, I would recommend spacing out the surgeries. Sometimes the implant will move around in the anterior chamber, but sometimes it will anchor into place. It is a point of discussion now.

R.A.L.: Lastly, let's talk about wish lists. What would you like to see for drug delivery?

L.J.K.: I would like the ability to put in multiple agents, so different complementary drug classes that lower IOP, and I would like to see the marriage of MIGS devices and drug delivery.

J.K.: I would like a product that is lasts a long time, stays in the anterior chamber or vitreous, does not affect vision, and completely dissolves or erodes.

S.T.: I would like to see improved patient education so that patients are aware that there is another way to treat glaucoma beyond eye drops, that there are procedures we can do instead.

E.R.C.: For me, it is all about the drop-free life. I would like to see control fully in the hands of the physician with controlled delivery of multiple agents.

R.A.L.: We'll stay tuned. ■

1. Glaukos' iDose TR demonstrates sustained IOP reduction and favorable safety profile over 36 months in phase 2b study [news release]. Glaukos. January 11, 2022. Accessed May 1, 2022. www.businesswire.com/news/home/20220111005492/en/Glaukos'-iDose-TR-Demonstrates-Sustained-IOP-Reduction-and-Favorable-Safety-Profile-Over-36-Months-in-Phase-2b-Study
2. Weinreb RN, Robinson MR, Dibas M, Stamer WD. Matrix metalloproteinases and glaucoma treatment. *J Ocul Pharmacol Ther*. 2020;36(4):208-228.

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